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The absolute oral bioavailability of selected drugs

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Abstract. Oral bioavailability is best defined as the rate and extent to which an active drug substance is absorbed and becomes available to the general circulation. This concept is discussed, along with several popular methods for determining absolute oral bioavailability. The absolute oral bioavailability of numerous drugs is reviewed and interspecies comparisons are made. In general, absolute oral bioavailability does not correlate well between species, though relative comparisons might be made.

Key words: absolute oral bioavailability – absorption – pharmacokinetics – metabolism

Introduction

The term bioavailability has a variety of definitions and for this reason it is important that it be defined in whatever context it is used. According to Wagner [1979], the FDA originally defined bioavailability as the rate and extent to which an active drug substance is absorbed and becomes available at the site of action. In contrast, realizing the difficulties in measuring drug at the site of action, the American Pharmaceutical Association defines bioavailability as the rate and extent to which an active drug substance is absorbed and becomes available to the general circulation. The latter definition is of more practical use because it permits a fairly simple experimental determination to be made. Recently, the FDA has considered adopting the American Pharmaceutical Association's definition. It is important to note bioavailability is not just a property of the drug itself, but also of the formulation in which the drug is delivered.

Two types of bioavailability will be discussed here. Relative bioavailability is a comparison of the extent and rate of absorption and systemic availability of a drug from two different dose forms and sometimes in comparison to two different routes of administration. Absolute oral bioavailability is a special case in which the extent and rate of absorption and systemic availability of an oral dose is determined relative to an intravenous dose. This review deals strictly with the concept of absolute oral bioavailability and how it is measured.

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A distinction should be made between absorption and bioavailability, because the terms are often incorrectly used interchangeably. For the purpose of this discussion, absorption is defined as the drug passing from the lumen of the gastrointestinal (GI) tract into the tissue of the GI tract. Once into the tissue, the drug is considered absorbed. On the other hand, for a drug to be bioavailable, it must reach the general circulation intact. This is more of a challenge, because once the drug is absorbed it must still pass through the GI tract tissue, the liver, and the lungs before it reaches the general circulation. First-pass metabolism or elimination [Pond and Tozer 1984] in any of these three tissues may destroy or remove a portion of the drug which was absorbed and therefore, reduce the drug's bioavailability. Therefore, on a quantitative basis, the difference between absorption and bioavailability is that amount which is removed or destroyed by first-pass elimination or metabolism. It is possible for a drug to be completely absorbed, yet be entirely destroyed or removed by first-pass metabolism or elimination, so that its absorption is 100% but its oral bioavailability is 0%. Earlier work on this concept was conducted by Harris and Riegelmann [1969] using the metabolism of acetylsalicylate in the dog as a model. The concept is more elegantly presented in the pharmacokinetics handbook by Ritschel [1986].

Methods for determining absolute oral bioavailability of non-prodrugs

By far the most popularly used method for determining absolute oral bioavailability is what will be referred to here as the blood area under the curve (AUC) method. For this method, a drug is administered intravenously and orally and the concentrations of drug in blood (or plasma) are measured at numerous time points.

The areas under the concentration-time curves are determined (for a discussion of AUC calculation methods, see Ritschel [1984]) and absolute oral bioavailability is calculated according to the following equation:

$$F = \frac{\text{blood AUC}_{po}}{\text{blood AUC}_{iv}} \times \frac{\text{DOSE}_{iv}}{\text{DOSE}_{po}} \qquad \text{(Equation 1)}$$

where F is absolute oral bioavailability and the dose is expressed on a per body wt. basis. The ratio term for the doses allows one to make a linear correction if the oral and intravenous dose levels were different. It is also possible to correct the absolute oral bioavailability for differences in half-life [Gibaldi and Perrier 1982], in which case the equation is:

$$F = \frac{\text{blood AUC}_{po}}{\text{blood AUC}_{iv}} \times \frac{\text{DOSE}_{iv}}{\text{DOSE}_{po}} \times \frac{\text{HL}_{iv}}{\text{HL}_{po}} \qquad \text{(Equation 2)}$$

This correction accounts for differences in the rates of elimination when the drug is administered by the two different routes [Gibaldi and Perrier 1982].

The blood AUC method is generally the method of choice for determinaton of drug availability to the general compartment because it measures drug directly within the systemic circulation. It is most accurate for those drugs which are distributed largely within the central compartment. For drugs with a large volume of distribution, it is less accurate, and should be used with caution.

Another method which is less commonly used is the urine drug excretion method. This method is similar to the blood AUC method, except that the drug concentration is measured in urine instead of blood. This method has the advantage that it is noninvasive. To determine absolute oral bioavailability by the urine drug excretion method, the drug is administered intravenously and orally and urine samples are collected until the drug has been substantially eliminated. Absolute oral bioavailability is then calculated to the equation:

$$F = \frac{\text{urine AUC}_{po}}{\text{urine AUC}_{iv}} \times \frac{\text{DOSE}_{iv}}{\text{DOSE}_{po}} \qquad \text{(Equation 3)}$$

One of the disadvantages of the urine drug excretion method is that its usefulness is limited to those drugs for which significant quantities of intact drug are eliminated in the urine. It should be used with caution for drugs which are eliminated only in small amounts in the urine, due to the inherent error involved in trying to measure small differences between small numbers. Since highly lipophilic drugs in general are not eliminated in the urine due to a high level of plasma protein binding, the urine drug excretion method is generally not useful for highly lipophilic drugs. The blood AUC method should be used instead.

The AUC ratio methods described above may also be applied to other body fluids, such as saliva [Sakai et al. 1983]. As with the urine drug excretion method, this method has the advantage of being noninvasive. However, the use of saliva and other body fluids besides blood is only valid if intact drug is found there in significant amounts.

It is also possible to measure bioavailability of a drug not based on its drug concentrations in blood or urine, but on an observed pharmacological response. This "pharmacodynamic method" may be used if analytical procedures are not available for the drug. It assumes that the active form is the unmetabolized parent drug. The resulting pharmacological availability may differ somewhat from absolute oral bioavailability, due to the fact that there is not always a direct linear relationship between drug concentration and effect. This concept is discussed in more detail by Ritschel [1984 and 1987]. It should be noted that the measurement of bioavailability using a pharmacological response does have the advantage of estimating the availability of the drug to its site of action, according to the FDA's original definition. Therefore, if the goal of an investigation is to measure the effects of different variables on the efficacy of a drug, the use of a pharmacological response may be the method of choice. However, the reader should note that measurements of pharmacological response are often imprecise, and for this reason, pharmacological availability measurements often have a high degree of variability.

In situations where it is not possible to measure intact drug in blood or urine, it is possible to use the concentration of a metabolite to estimate the bioavailability of the parent compound [Wagner 1972]. For this calculation, the assumption is made that metabolism of parent compound to the metabolite is the same for either the intravenous or oral routes of administration. This should be validated prior to using this method, particularly if the drug undergoes first-pass metabolism, because if the metabolite is produced by first-pass metabolism, the absolute oral bioavailability will be overestimated by this method.

It should be emphasized that the methods described above for determining absolute oral bioavailability are really estimates, based on the assumptions that the volumes of distribution, clearance rates, and half-lives for the drug are the same following intravenous and oral administration. These estimates also make the assumptions that the drug does not exhibit saturable metabolism within the range of the doses tested and that the routes of metabolism are constant as the route of administration is varied. If any of these assumptions are not met, then the estimation of absolute oral bioavailability by these methods may be somewhat in error. A number of investigators have proposed models for more accurate determination of absolute oral bioavailability when these assumptions are not met [Rubin and Tozer 1984, Kwan and Till 1973, Collier and Riegelman 1983].

It is often desirable to estimate what the absolute oral bioavailability might be, even though oral dosing data are not available. According to the method of Gibaldi et al. [1971], this can be done if one assumes that absorption is complete and that the loss of drug occurs only due to first-pass metabolism in the liver. It requires an estimate of the blood flow rate to the liver. The equation used is:

$$F = \frac{Q}{Q + D/AUC} \qquad \text{(Equation 4)}$$

where Q is the liver blood flow, D is the dose administered intravenously, and AUC is the area under the intravenous concentration-time curve for intact drug. For drugs which are distributed into the plasma (as opposed to the blood cells), a more accurate estimate may be obtained if plasma concentrations are used to calculate the AUC and Q is expressed as plasma flow rate rather than blood flow rate.

Methods for determining absolute oral bioavailability of prodrugs

Prodrugs [Stella et al. 1985] present a special case for measuring bioavailability because the administered drug is not the active form. It would, therefore, be misleading to calculate the bioavailability according to concentrations of the intact prodrug in blood. It is preferable to measure the concentrations of the active form after administration of the prodrug by the intravenous and oral routes. The oral bioavailability could then be estimated using Equation 1. However, this may lead to an overestimation of bioavailability if all or a portion of the active form is generated by a first-pass mechanism. In this case, one should administer the active drug by the intravenous route and the prodrug by the oral route. The active drug should then be measured in blood or urine, and the oral bioavailability calculated using Equation 1. In this way, the ammount of active drug formed from the orally administered prodrug is compared to an intravenous dose of active drug, which is by definition 100% bioavailable.

Drugs with active metabolites

In cases where the pharmacological activity of a drug is due to multiple circulating active forms, measurement of bioavailability becomes a tricky issue. In some cases, it has been possible to measure the concentrations and relative activities of several contributing metabolites [Marino et al. 1986]. However, this is an arduous task and it involves assumptions which may not be met. In situations such as this, it may be possible to use a single major metabolite to estimate bioavailability. A pharmacological endpoint may also provide a viable alternative for measuring drug bioavailability under these circumstances.

Factors affecting the measurement of absolute oral bioavailability

There are a variety of factors which could affect the assessment of absolute oral bioavailability, and a detailed discussion of each would be beyond the scope of this review. More information on these factors may be found in the reviews by Ritschel [1987a and b], Jollow and Brodie [1972], Pond and Tozer [1984], Melander and McLean [1983] and Bauer et al. [1984]. Several of these factors will, however, be mentioned here as a reminder of the complexity of biological systems.

Obviously, various disease states such as hepatic failure may have major effects on absolute oral bioavailability. This will especially be the case if the drug undergoes first-pass metabolism. For a drug which is administered as the active form, hepatic failure would lead to decreased first-pass metabolism and hence increased bioavailability. However, in the case of a prodrug which is activated by first-pass metabolism, hepatic failure would result in decreased bioavailability.

Strictly speaking, one would not expect renal failure to have a large impact on absolute oral bioavailability, because the effect of renal failure should be similar, regardless of whether the drug was administered orally or intravenously. However, if renal elimination is dose-dependent, renal failure may lead to an apparent change in absolute oral bioavailability if the amount of drug delivered to the systemic circulation following intravenous dosing is different than the amount delivered following oral dosing.

The rate of drug dissolution and drug absorption are important determinants of bioavailability [Jollow and Brodie 1972], particulary for drugs which undergo saturable first-pass metabolism. It follows that characteristics of the gastrointestinal tract such as motility, pH, feeding state and the presence of bile salts would have an effect on drug bioavailability. It would, therefore, be expected that altered GI function may have an impact on bioavailability. This will especially be the case for drugs which undergo first-pass metabolism within the GI tract tissue.

Diurnal variation may have an impact on the measurement of absolute oral bioavailability. It has been reported [Bauer et al. 1984] that such diurnal changes in bioavailability may be due to diurnal changes in drug clearance, among other things.

Absolute oral bioavailability – a review of the published data

For this review, absolute oral bioavailability data on over 400 drugs was collected. The data are shown in Tables 1 and 2. By far, the bulk of the information collected has been obtained in man, but some data are available for experimental animals as well.

The absolute oral bioavailabilities in man range from near zero (buspirone, cephacetrile, cephalothin, cephapirin, cimetropium bromide, coumarin and isoproterenol) to complete (amosulalol, caffeine, cephalexin, diflusinal, ethosuximide, indomethacin, minocycline, pentobarbital, piroxicam, practolol, probenecid and trimethoprim, to name a few). However, most drugs are somewhere in between. Figure 1 shows the frequency distribution of the absolute oral bioavailability of drugs in humans. Surprisingly, the distribution is quite flat, but skewed slightly toward complete bioavailability. It should be noted that this population of data is almost certainly biased, since it represents only those data reported in the literature. There might be numerous drugs whose development was abandoned due to low bioavailability, and for

Table 1. Percent absolute oral bioavailability of drugs. Absolute oral bioavailability has been determined for these drugs by comparison of the plasma or urinary AUCs for intact drug. For the prodrugs which are reported in this table, the bioavailability calculation was done using concentrations of the unconverted prodrug.

Drug	Rodents	Dogs	Primates	Man	References
Acebutolol				37±12	Benet et al. 1984, Meier 1982
Acetaminophen				72±11	Amlie et al. 1979, Clements et al. 1984, Divoll et al. 1982, Forrest et al. 1982
Acetylmethadol	60±8[a]				Henderson et al. 1977
Acetylnormethadol			16±2[b]		Misra et al. 1980
Acetylprocainamide	84–100[a]			92±9	Kamath et al. 1981, Strong et al. 1975, Jacobi et al. 1983
Acetylsalicylate	35[a]	45±8		46–68	Harris and Riegelman 1969, Iwamoto et al. 1982, Needs and Brooks 1985 Pedersen and FitzGerald 1984
Acidocillin				74	Simon et al. 1976
Acyclovir		80–90		15–50	Krasny et al. 1981, Laskin 1983, Peterslund et al. 1984
Alclofenac	88[c]			36–96	Testa et al. 1978, Verbeeck et al. 1983
Alizapride				75–93	Houin et al. 1984
Allopurinol				90±9	Breithaupt and Tittel 1982, Murell and Rapeport 1986
Alprazolam				88	Smith et al. 1984
Alprenolol				9±6	Johnsson and Regardh 1976
Amantadine				95±5	Benet et al. 1984
Amiodarone				22–86	Latini et al. 1984, Pourbaix et al. 1985, Riva et al. 1982
Amitriptyline				46±9	Pond and Tozer 1984, Schulz et al. 1985
Amlodipine				52–88	Faulkner et al. 1986
Amosulalol				100	Nakashima et al. 1984
Amoxicillin				93±10	Arancibia et al. 1980, Spyker et al. 1977
Amphotericin B				<10	Benet et al. 1984
Ampicillin				62±17	Ehrnebo et al. 1979, Tanigawara et al. 1982
Amrinone				93±12	Park et al. 1983
Amsacrine	90±10[c]				Paxton 1986
Aprinidine				85–95	Benet et al. 1984
Atenolol				54±12	Fitzgerald et al. 1978, Johnsson and Regardh 1976, Mason et al. 1979 Meier 1982, Wan et al. 1979
Azosemide				10	Brater et al. 1983
Benzidamine				59–128	Taylor et al. 1987
Benznidazole		130			Workman et al. 1984
Bepridil				60	Benet 1985
Betaxolol				90	Warrington et al. 1980
Biperiden				33±5	Grimaldi et al. 1986
Bretylium				12–37	Garrett et al. 1982, Rapeport 1985
Bromocriptine	6[a]				Schran et al. 1985
Bromopride				49	Brodie et al. 1986
Brotizolam				70±22	Jochemsen et al. 1983 a and b
Budesonide				11±4	Ryerfeldt et al. 1982
Buflomedil				50–80	Clissold et al. 1987
Bufuralol				46±15	Dayer et al. 1982, Tschopp et al. 1978
Bumetanide				66±11	Holazo et al. 1984, Lau et al. 1986
Bupropion				60–80	Benet et al. 1984
Buspirone				3	Gammans et al. 1986
Butylmorphine	10[a]				Butz et al. 1985

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Caffeine				100	Blanchard and Sawers 1983
Canrenoate				100	Beermann and Groschinsky-Grind 1980
Captopril	39–59[a,d]			62	Duchin et al. 1982, Singhvi et al. 1981
Carbamazepine				70	Benet et al. 1984
Carbenicillin				<10	Benet et al. 1984
Carbidopa		88			Obach et al. 1984
CB-1954		40±7			Workman et al. 1986
Cefaclor				90	Benet et al. 1984
Cefadroxil				78–90	Marino et al. 1982
Cefalexin				80–100	Brogard et al. 1978
Cefamandole				96±3	Benet et al. 1984
Cefatrizine				55–77	Pfeffer et al. 1983
Cefoperazone				<10	Benet et al. 1984
Cefoxitin		8±2		78	Benet et al. 1984, Fix et al. 1986
Ceftazidime				<10	Benet et al. 1984
Cefuroxime				1	Foord 1976
Cefuroxime Axetil				23–44	Williams and Harding 1984
Cephacetrile				0	Brogard et al. 1978
Cephalexin				120±16	Schneider et al. 1978
Cephalothin				0	Brogard et al. 1978
Cephapirin				0	Brogard et al. 1978
Cephradine				85±29	Brogard et al. 1978, Philipson et al. 1987, Rattie et al. 1976
Chloprednol				93–99	Mroszcak et al. 1978
Chlorambucil				73–102	Newell et al. 1983
Chloramphenicol				69±13	Ambrose 1984, Kauffman et al. 1981, Kramer et al. 1984, Nahata and Powell 1981
Chloramphenicol Palmitate				80	Ambrose 1984
Chlordiazepoxide				100	Greenblatt et al. 1978
Chlormethiazole				12±3	Blaschke and Rubin 1979, Pentikainen et al. 1978, Pond and Tozer 1984
Chloroquine	69[c]			89–98	Aderounmu et al. 1987, Gustafsson et al. 1983
Chlorothiazide		70+18		33–56	Osman et al. 1982, Resetarits and Bates 1979
Chlorpheniramine	11+8[c]	30–50		25–44	Athanikar and Chiou 1979, Huang et al. 1981 and 1982, Paton and Webster 1985
Chlorpromazine				32±19	Benet et al. 1984
Chlorpropamide				118	Huupponen and Lammintausta 1981
Chlorprothixene				41±21	Roaflaub 1975
Chlortetracycline				25–30	Fabre et al. 1971
Chlorthalidone				64±10	Beermann and Groschinsky-Grind 1980, Fleuren et al. 1979
Cicloprolol				100	Dubruc et al. 1987
Cimetidine				60±10	Arancibia et al. 1985, Bodemar et al. 1981, Okolicsanyi et al. 1982, Richards 1983, Somogyi and Gugler 1983, Somogyi et al. 1980
Cimetropium Bromide				2±1	Imbimbo et al. 1986
Cinromide			35–79[b]		Lane and Levy 1983
Ciprofloxacin				63–77	Hoffken et al. 1985
Cisapride				40–50	Van Peer et al. 1987
Clavulanate				31–99	Bolton et al. 1986, Davies et al. 1985, Nilsson-Ehle et al. 1985

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